Br J Vener Dis 1984;**60**:243-8

Sexual behaviour of women with human papillomavirus (HPV) lesions of the uterine cervix

K SYRJÄNEN,* M VÄYRYNEN,† O CASTRÉN,† M YLISKOSKI,†
R MÄNTYJÄRVI,‡ S PYRHÖNEN,§ AND S SAARIKOSKI†

*From the *Department of Pathology, University of Kuopio, the †Department of Gynaecology and Obstetrics, Kuopio University Central Hospital, the ‡Department of Clinical Microbiology, University of Kuopio, Kuopio, and the §Department of Virology, University of Helsinki, Helsinki, Finland*

SUMMARY To analyse the epidemiological aspects contributing to the transmission of human papillomavirus (HPV) lesions (flat, inverted, and papillomatous condylomas) of the uterine cervix, we recorded the sexual behaviour of 146 women who consecutively attended the department of obstetrics and gynaecology of Kuopio University Central Hospital with a cervical HPV lesion (with or without concomitant cervical intraepithelial neoplasia (CIN)). Similar data were collected from an age matched group of women with no signs of gynaecological infection. The sexual habits of the women infected with HPV differed from those of healthy controls in most aspects studied, including an earlier onset of sexual activity ($p<0\cdot05$), lower number of deliveries ($p<0\cdot05$), less regular use of contraceptive measures ($p<0\cdot05$), and use of the condom instead of intrauterine contraceptive device (IUCD) ($p<0\cdot0001$). They also differed from controls in giving histories of more frequent episodes of: CIN ($p<0\cdot005$), abnormal Pap (Papanicolaou) smears ($p<0\cdot0001$), sexually transmitted disease (STD) ($p<0\cdot05$), and genital warts ($p<0\cdot001$). Furthermore, they had more multiple sexual partnerships (both past and current) than the controls ($p<0\cdot0001$ and $0\cdot005$ respectively), they had not established permanent partnerships as often as the controls ($p<0\cdot001$), and they had a higher frequency of casual relationships ($p<0\cdot0001$). In addition, their own and their partners' sexual hygiene was poorer than in the control subjects ($p<0\cdot05$ and $0\cdot001$ respectively). The results show the dramatic influence of sexual behaviour on the transmission of cervical HPV lesions, which are known to be intimately associated with CIN in many cases.

Introduction

For some time sexual promiscuity and early onset of sexual activity have been considered to be responsible for the observed increase of cervical intraepithelial neoplasia (CIN) in very young girls.[1-8] CIN in turn is known to proceed to an invasive carcinoma within varying periods of time.[9 10] Not surprisingly many authors are convinced that carcinoma of the uterine cervix is a sexually transmitted disease (STD), probably caused by a virus.[7 11-16] This hypothesis has recently gained support from reports linking cervical and penile cancer and emphasising the role of high risk men in the aetiology of cervical cancer.[17-23]

Since the 1960s, the transmissible agent blamed for the development of cervical cancer has been herpes simplex virus (HSV).[6 7 12 13] It was not until 1976 that the possible role of human papillomavirus (HPV) was explored.[24 25] Since then, this theory has gained substantial support from the observations on the new types of HPV lesions (flat and inverted condylomas), which have been reported to be closely associated with CIN and even with invasive cervical carcinomas.[26-32] At the moment, HPV seems to be the agent most likely to cause uterine cervical carcinoma.[25-35]

The natural history of the classic papillomatous genital wart (condyloma acuminatum) as an STD induced by HPV is well recognised.[25 34-38] The peak incidence of condyloma acuminatum coincides with the period of maximum sexual activity.[36-38] Little is known about the natural history of the newly described flat and endophytic condylomas[38] shown to be intimately associated with CIN.[24 26-30 32]

Address for reprints: Dr K Syrjänen, Senior Lecturer, Department of Pathology, University of Kuopio, P O Box 6, SF-70211 Kuopio 21, Finland

Accepted for publication 30 November 1983

As a part of a long term follow up study of women with cervical HPV lesions that is currently in progress in our clinic, we report on the sexual habits of such women to provide evidence of the influence of sexual behaviour on the development and spread of this increasingly common infection.

Materials and methods

We studied the first 146 consecutive women included in our prospective follow up study of women with an HPV (flat, inverted, or papillomatous) lesion of the uterine cervix. The present study was set up to assess the natural history (and all factors influencing it) of these HPV lesions and concomitant CIN changes that are unaffected by any kind of treatment. During this study, the women attended the outpatient department of obstetrics and gynaecology, Kuopio University Central Hospital, at six month intervals. At each visit the patients underwent colposcopy and either a biopsy or a Pap (Papanicolaou) smear. In addition, material was taken from the cervix for microbiological examination, and a blood sample was collected for immunological analysis.

The patients had been selected for the prospective follow up study on the basis of a Pap smear suggesting HPV.[24 30] On their first attendance at the hospital, the diagnosis was confirmed by colposcopy and biopsy examination, using the criteria described previously.[26-29 32] All the patients included in the present study had a definite HPV (flat, inverted, or papillomatous) lesion of the uterine cervix, either with or without concomitant CIN.

During their first clinic visit, all the women were asked to answer an extensive questionnaire to give data of possible epidemiological relevance to their HPV infection and its transmission, which included their previous gynaecological and obstetric history, their medical history, and any history of STD. Data concerning their sexual partners and technical aspects of their sexual intercourse were also recorded in detail. To facilitate the acceptability of this inquiry the questionnaire was completed anonymously.

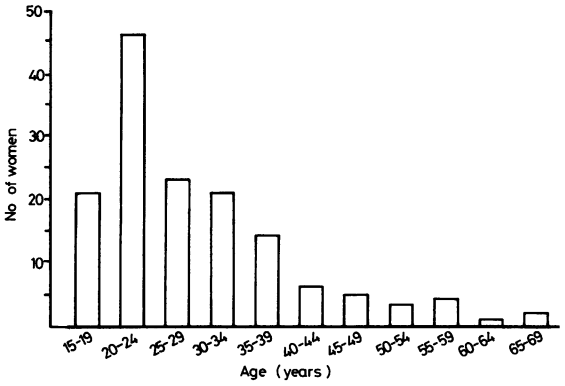

FIGURE *Age distribution of the women studied in two age matched groups.*

To extract the data pertinent to the epidemiology of HPV infection and its transmission, the same questions were presented to an age matched series of healthy women without any signs of HPV infection of the uterine cervix. This was accomplished by mailing the questionnaire to a randomly selected series of women who had normal Pap smears. (The Pap smears of the patients with HPV and the controls were examined by the pathologist at the laboratory of pathology, Finnish Cancer Society, Kuopio). From this series, every patient with HPV was matched by age with a control in an otherwise completely random manner. The present report is based on questionnaires answered by two age matched groups of 146 women, one group with cervical HPV infection and the other without any signs of a genital infection. The age distribution of both groups of women is shown in the figure.

TABLE I *Comparison of gynaecological and obstetric histories of controls and women with HPV infections*

	Controls (n = 146)	*Patients with condylomas (n = 146)*	*Significance*
Mean (SD) age (years)	29·1 (10·7)	28·7 (10·3)	NS
Mean (SD) age at menarche (years)	13·3 (1·3)	13·2 (1·4)	NS
No menstruating regularly	93	88	NS
No menstruating irregularly	53	58	NS
Mean (SD) No of pregnancies	2·53 (1·49)	2·27 (1·41)	NS
Mean (SD) No of deliveries	2·09 (1·32)	1·68 (1·29)	0·05
Mean (SD) No of miscarriages	0·19 (0·49)	0·18 (0·44)	NS
Mean (SD) No of abortions	0·24 (0·48)	0·36 (0·62)	NS
Mean (SD) age at first coitus (years)	18·1 (2·9)	17·5 (2·6)	0·05
Mean (SD) years of active sexual life	10·9 (9·0)	11·5 (9·9)	NS
No regularly using contraception:	119	85	0·05
Oral contraceptive	51	42	NS
Condom	17	23	0·05
Intrauterine contraceptive device	55	27	0·001
Sterilised	3	4	NS
Other contraceptive	2	4	NS

TABLE II *Medical histories of controls and women with HPV infections*

	Controls (n = 146)	*Patients with condylomas (n = 146)*	*Significance*
Previous cervical intraepithelial neoplasia	0	7	0·005
During the past year	0	3	NS
1-2 years ago	0	3	NS
2-4 years ago	0	1	NS
Regular cervical cytological examination	78	75	NS
Date of last Pap smear			
First smear	12	5	NS
During the past year	35	59	0·005
1-2 years ago	50	38	NS
2-4 years ago	16	18	NS
More than 5 years ago	3	6	NS
No data	30	20	NS
Last Pap smear normal	111	61	0·0001
Previous radiotherapy	0	0	NS
Current treatment			
Insulin	0	1	NS
Oral hypoglycaemic agents	1	0	NS
Steroids	5	5	NS
Other immunosuppressive agents	0	1	NS

For the statistical calculations, Student's *t* test and the χ^2 test were used.

Results

Table I gives a summary of the gynaecological and obstetric history of the patients with HPV and the controls. The two groups differed from each other in the mean number of deliveries ($p<0·05$), the mean age of first coitus ($p<0·05$), and the regularity and type of contraception used. The women in the control group used an intrauterine contraceptive device (IUCD) more frequently than those with HPV ($p<0·001$) and a condom less frequently ($p<0·05$).

Table II shows the medical history of the women in the two groups. Those with HPV were more likely to have had CIN, to have had a recent Pap smear, and to have had an abnormal Pap smear result at their most recent examination (excluding the one by which the patient was entered into the study). The two groups did not differ from each other in current treatment of illnesses unrelated to HPV.

Table III shows histories of STD in both groups. The women with HPV were more likely than the controls to have had STD ($p<0·05$), and significantly more frequently had had warts especially genital warts ($p<0·001$). The two groups did not differ in respect of a history of warts in their sexual partners.

Table IV summarises the sexual relationships of the women in the two groups, who behaved differently in most respects. These included changes of previous as well as current sexual partners, establishing a permanent (over four years' duration) relationship, the mean number of partners within the past two years, and the occurrence of casual relationships.

Table V shows the data concerning the sexual habits of the women. Those with HPV practised intercourse on more occasions but less regularly than the controls ($p<0·05$). Both groups were similar with

TABLE III *Comparison of histories of sexually transmitted disease in controls and women with HPV infections*

	Controls (n = 146)	*Patients with condylomas (n = 146)*	*Significance*
Previous sexually transmitted diseases	2	8	0·05
Gonorrhoea	1	7	0·05
Chlamydia	1	1	NS
Syphilis	0	0	NS
Warts in sexual partners:	9	17	NS
Genitalia	2	6	NS
Mouth	0	1	NS
Hand	7	10	NS
Previous warts in patient	21	43	0·005
Genitalia	2	18	0·001
Mouth	0	3	NS
Skin	20	27	NS
Anus	2	4	NS

TABLE IV *Comparison of data on sexual partners of women with HPV and controls*

	Controls (n = 146)	*Patients with condylomas (n = 146)*	*Significance*
Current sexual partner unchanged (during past 2 years)	143	131	0·005
Current sexual partner since:			
Less than 1 year ago	18	33	0·025
1-3 years ago	27	46	0·01
4-6 years ago	39	13	0·001
More than 6 years ago	57	33	0·005
Previous sexual partner (excluding past 2 years) unchanged	112	73	0·0001
Frequency of change of previous sexual partners:			
Less than once a year	15	20	NS
1-3 partners a year	12	34	NS
4-6 partners a year	5	11	NS
More than 6 partners a year	1	7	NS
Mean (SD) No of sexual partners in past 2 years	1·31 (1·31)	2·22 (2·56)	0·001
Casual sexual partners:	5	26	0·0001
Foreign	0	1	NS
Domestic	5	25	0·0001

regard to the types of intercourse practised, but took more care over their own and their partners' sexual hygiene.

Discussion

HPV comprises a heterogeneous group of viruses, with at least 25 different types being recognised at the moment.[33-35] Each HPV type seems to have a predilection for a particular site of infection, genital warts being associated with HPV6 and HPV11.[33] Flat and inverted HPV lesions of the uterine cervix,[24] have been repeatedly connected with CIN, and HPV is currently regarded as a potential aetiological agent of cervical carcinoma.[25-33 35] It is accepted that condyloma acuminatum (mostly due to HPV6) is an STD, its incidence coinciding with peaks of sexual activity and promiscuity.[36-38] The age distribution of patients with flat and inverted condylomas parallels that of those with condyloma acuminatum,[26-32] but so far the association of HPV with sexual promiscuity has been speculative.[32 38] This sexual behaviour has also been blamed for the increased incidence of atypical Pap smears and CIN reported in young age groups.[1-8] There seem to be many similarities between the epidemiology of condyloma acuminatum and cervical cancer, which is regarded by many as an STD.[7 11-16] Whether this epidemiological similarity also holds true of the flat and inverted condylomas was the main topic of the present study. That this could be the case is suggested by the recent findings of HPV16 and HPV18 deoxyribonucleic acid (DNA) in more than 80% of cervical carcinomas studied, thus creating the concept of high risk HPV types (16 and 18) and low-risk types (6 and 11).[33]

As has been repeatedly emphasised, the only way to assess the clinical behaviour of HPV lesions is to conduct a prospective follow up study.[25 27-29 31 32] As a

TABLE V *Comparison of data on sexual habits of women with HPV and controls*

	Controls (n = 146)	*Patients with condylomas (n = 146)*	*Significance*
Regular sexual intercourse	79	55	0·005
Mean (SD) frequency of intercourse/week	2·20 (1·43)	2·63 (2·01)	0·05
Type of sex practised:			
Cunnilingus	77	77	NS
Fellatio	76	86	NS
Anal	13	16	NS
Above type of sex practised:			
Regularly	23	17	NS
Frequently	12	20	NS
Seldom	46	49	NS
Not specified	7	7	NS
No data	6	5	NS
Personal hygiene before intercourse:			
Good	113	93	0·05
Poor	28	43	0·05
Partners' personal hygiene before intercourse:			
Regularly good	86	44	0·0001
Occasionally good	96	64	0·001

part of such a study in our clinic, the sexual behaviour of these patients was recorded for the first time. As shown in the figure, the age distribution of the patients studied is identical with that of other reports.[31] [32] Most of the cervical HPV lesions occurred in women under 30 (mean 28·7) years with peak incidence in the 20-24 year old group. This paralleled the earlier onset of sexual activity in such women ($p<0·05$) (table I). The women in the control group had significantly more deliveries ($p<0·05$) than the HPV patients despite having the same number of pregnancies. This was due to a greater number of abortions (table I), and seemed to reflect the more permissive sexual habits and less regular and permanent sexual relationships of the women with HPV. Contraceptive measures were less frequently used by women with HPV than by controls ($p<0·05$). Furthermore, the less frequent use of an IUCD but more of the condom reflects the different attitudes to contraception of these two groups of women (table I).

With regard to their medical histories, none of the women in the control group had had CIN, whereas seven of the HPV patients had ($p<0·005$). This is consistent with previous suggestions that early onset of sexual activity and promiscuous sexual habits predispose to the development of CIN.[1-8] This should encourage an increased demand for cervical cytology tests,[39] as was shown in this study by the increased numbers of recent (within the last year) Pap smears in women with HPV (table II). Consistently with the above views, the latest Pap smear in this group of women was abnormal significantly more frequently ($p<0·0001$) (table II) than in the controls. The failure to find any appreciable difference in previous and current treatment including immunosuppression, which is known to predispose to warts,[40] suggests that immunosuppression is not a major factor contributing to the development of cervical HPV (table II).

As pointed out in the classic paper by Oriel,[36] the onset of genital warts parallels that of gonorrhoea. This was also the case in this study (table III), and patients with HPV gave a history of gonorrhoea significantly more frequently than the control women. On the other hand, no direct correlation could be established between cervical HPV and a history of cutaneous warts (table III). This confirms the results of Oriel, who did not find any epidemiological evidence of a close relation between genital and skin warts,[36] and it has been established recently that these two lesions are caused by completely different types of HPV.[34] [35] [40] The women with HPV were more likely to have been treated previously for genital warts than the controls ($p<0·001$), which supports the theory that external genital warts are frequently accompanied or followed by lesions in the uterine cervix.[25] [32] [37] [38] Women with external genital warts should therefore be screened for cervical lesions.

This study confirms the association of promiscuity with HPV and CIN (table IV). Women with HPV changed their sexual partners significantly more often than controls, and controls had established permanent (over four years' duration) sexual partnerships significantly more frequently than the patients with HPV (table IV). This is shown by the mean numbers of sexual partners within the past two years. Similarly, the numbers of casual sexual contacts were exceedingly low in the control group (only 3·4%) compared with those of women with HPV (17·8%). These data agree with the current concepts that genital warts are sexually transmitted, being found in female contacts of men with genital warts.[36-38] This now seems to be established for the flat and inverted HPV lesions, which outnumbered the classic papillomatous ones in this study. The present study did not, however, establish a direct relation between the genital warts (visible ones) of the sexual partners and current HPV lesions in the women (table III). This is probably due to the failure of the women to remember how many of their partners had genital warts. The other, and perhaps even more important, explanation is that we do not currently recognise a counterpart of the flat and inverted HPV lesions, which may well exist in men. This emphasises the validity of the concept of high risk men,[22] and we would advocate the study of the male partners of women infected with HPV.

Data on sexual habits show some pronounced differences between the two groups of women (table V). Intercourse was more often regular in the control group (mostly married) than in women with HPV, although the frequency of intercourse was higher in the latter. The types of sexual intercourse practised did not vary between the two groups. This could indicate that, generally speaking, anal and oral sex is not as important a source of HPV infection as is conventional coitus. That promiscuous sexual behaviour frequently goes hand in hand with poor sexual hygiene is clearly demonstrated in the present survey (table V). Good personal hygiene was almost the rule in the control group, but not in patients with HPV. The same seems to be true of their partners' sexual hygiene. The reason most frequently reported by the women with HPV was the lack of appropriate facilities. This reflects their lower socioeconomic status and the nature of the places where they practised sexual acts.

Most of the above data are familiar from the extensive surveys on risk factors of cervical cancer, including early onset of sexual activity (age at first

coitus), multiple partners, poor sexual hygiene, and low socioeconomic status.[1-4 6-8 11-14] These data are confirmed by those obtained in this study of women with cervical HPV with or without CIN. In most respects our results show that the sexual habits of healthy women without any signs of HPV infection are noticeably different from those with a cervical HPV lesion. These epidemiological data show the crucial influence of sexual behaviour on the transmission of all types (flat, inverted, or papillomatous) of cervical HPV lesions associated (by morphology, immunology, and molecular biology) with the development of CIN and cervical cancer.[26-29 31-35] This further emphasises the significance of HPV as a potential cause of cervical cancer, and justifies the concept of all women infected with HPV as high risk patients.

This study was supported in part by a research grant (07/014) from the Medical Research Council of the Academy of Finland, and in part by a research grant from the Finnish Cancer Society.

References

1. Andrews FJ, Linehan JJ, Melcher DH. Cervical cancer in younger women. *Lancet* 1978;ii:776-8.
2. Feldman MJ, Linzey EM, Srebnik E, Kent DR, Goldstein AI, Nelson M. Abnormal cervical cytology in the teen-ager: a continuing problem. *Am J Obstet Gynecol* 1976;**126**:418-21.
3. Feldman MJ, Kent DR, Pennington RL. Intraepithelial neoplasia of the uterine cervix in the teenager. *Cancer* 1978;**41**:1405-8.
4. King JFW. Sexual activity as environmental cancer hazard. *N Y State J Med* 1980;**80**:1253-8.
5. Roddick JW. Gynecologic disease in young, sexually active women. *Am J Obstet Gynecol* 1976;**126**:880-9.
6. Rotkin ID. Adolescent coitus and cervical cancer: associations of related events with increased risk. *Cancer Res* 1967;**27**:603-17.
7. Rotkin ID. A comparison review of key epidemiological studies in cervical cancer related to current searches for transmissible agents. *Cancer Res* 1973;**33**:1353-1567.
8. Snyder RN, Ortiz Y, Willie S, Cove JKJ. Dysplasia and carcinoma in situ of the uterine cervix: prevalence in very young women (under age 22). *Am J Obstet Gynecol* 1976;**124**:751-6.
9. Johnson LD, Nickerson RJ, Easterday CL, Stuart RS, Hertig AT. Epidemiologic evidence for the spectrum of change from dysplasia through carcinoma in situ to invasive cancer. *Cancer* 1968;**22**:901-14.
10. Richart RM, Barron BA. A follow-up study of patients with cervical dysplasia. *Am J Obstet Gynecol* 1969;**105**:386-93.
11. Beral V. Cancer of the cervix: a sexually transmitted infection? *Lancet* 1974:i:1037-40.
12. Kessler II. Human cervical cancer as a venereal disease. *Cancer Res* 1976;**36**:783-91.
13. Kessler II. Venereal factors in human cervical cancer. Evidence from marital clusters. *Cancer* 1977;**39**:1912-9.
14. Meisels A, Bégin R, Schneider V. Dysplasias of uterine cervix. Epidemiological aspects: role of age at first coitus and use of oral contraceptives. *Cancer* 1977;**40**:3076-81.
15. Munoz N. Model systems for cervical cancer. *Cancer Res* 1976;**36**:792-3.
16. Richardson AC, Lyon JB. The effect of condom use on squamous cell cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 1981;**140**:909-13.
17. Cocks PS, Adib RS, Hunt KM. Concurrent carcinoma of penis and carcinoma-in situ of the cervix in a married couple. Case report. *Br J Obstet Gynaecol* 1982;**89**:408-9.
18. Goldberg HM, Pell-Ilderton R, Daw E, Saleh N. Concurrent squamous cell carcinoma of the cervix and penis in a married couple. *Br J Obstet Gynaecol* 1979;**86**:585-6.
19. Graham S, Priore R, Graham M, Browne R, Burnett W, West D. Genital cancer in wives of penile cancer patients. *Cancer* 1979;**44**:1870-4.
20. Martinez I. Relationship of squamous cell carcinoma of the cervix uteri to squamous cell carcinoma of the penis among Puerto Rican women married to men with penile carcinoma. *Cancer* 1969;**24**:777-80.
21. Reddy CRRM, Rao TG, Venkatarathnam G, Kameswari VR, Sashiprabha R, Raghavaiah NV. A study of 80 patients with penile carcinoma combined with cervical biopsy of their wives. *Int Surg* 1977;**62**:549-53.
22. Singer A, Reid BL, Coppleson M. A hypothesis: the role of a high-risk male in the etiology of cervical carcinoma. *Am J Obstet Gynecol* 1976;**126**:110-5.
23. Smith PG, Kinlen LJ, White GC, Adelstein AM, Fox AJ. Mortality of wives of men dying with cancer of the penis. *Br J Cancer* 1980;**41**:422-8.
24. Meisels A, Fortin R. Condylomatous lesions of the cervix and vagina. I. Cytologic patterns. *Acta Cytol (Baltimore)* 1976;**20**:505-9.
25. zur Hausen H. Human Papillomaviruses and their possible role in squamous cell carcinomas. *Curr Top Microbiol Immunol* 1977;**78**:1-30.
26. Syrjämem KJ. Morphologic survey of the condylomatous lesions in dysplastic and neoplastic epithelium of the uterine cervix. *Arch Gynaekol* 1979;**227**:153-61.
27. Syrjänen KJ. Condylomatous lesions in dysplastic and neoplastic epithelium of the uterine cervix. *Surg Gynecol Obstet* 1980;**150**:372-6.
28. Syrjänen KJ. Condylomatous epithelial changes in uterine cervix and their relationship to cervical carcinogenesis. *Int J Gynaecol Obstet* 1980;**17**:415-20.
29. Syrjänen KJ. Current views on the condylomatous lesions in uterine cervix and their possible relationship to cervical squamous cell carcinoma. *Obstet Gynecol Surv* 1980;**35**:685-94.
30. Syrjänen KJ, Heinonen U-M, Kauraniemi T. Cytological evidence of the association of condylomatous lesions with the dysplastic and neoplastic changes in uterine cervix. *Acta Cytol (Baltimore)* 1981;**25**:17-22.
31. Syrjänen KJ. Human Papillomavirus (HPV) lesions in association with cervical dysplasias and neoplasias. *Obstet Gynecol* 1983;**62**:617-24.
32. Meisels A, Morin C. Human papillomavirus and cancer of the uterine cervix. *Gynecol Oncol* 1981;**12**:111-23.
33. Gissmann L, Dürst M, Ikenberg H. Presence of HPV DNA in human genital carcinomas. *Proc Natl Acad Sci USA* 1983;**80**:3812-4.
34. Howley P. The human papillomaviruses. *Arch Pathol Lab Med* 1982;**106**:429-32.
35. zur Hausen H, Gissmann L. Papillomaviruses. In: Klein G, ed. *Viral Oncology*. New York: Raven Press, 1980; 433-45.
36. Oriel JD. Natural history of genital warts. *Br J Vener Dis* 1971;**47**:1-13.
37. Oriel JD. Genital warts. *Sex Transm Dis* 1977;**4**:153-9.
38. Oriel JD. Genital warts. *Sex Transm Dis* 1981;**8**:326-9.
39. Fields C, Restivo RM, Brown MC. Experience in mass Papanicolaou screening and cytologic observations of teen-age girls. *Am J Obstet Gynecol* 1976;**124**:730-4.
40. Jablonska S, Orth G, Lutzner MA. Immunopathology of papillomavirus-induced tumors in different tissues. *Springer Semin Immunopathol* 1982;**5**:33-62.